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Possible New Autosomal Recessive Syndrome of Lymphedema, Hydroceles, Atrial Septal Defect, and Characteristic Facial Changes

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We describe two brothers with congenital lymphedema of lower limbs, atrial septal defect (ASD), and similar facial appearance. A sister had severe hydrops fetalis, ASD, omphalocele, and other anomalies. This combination of congenital lymphedema and ASD differs from other reported cases of congenital lymphedema and most likely constitutes a previously unrecognized autosomal recessive syndrome. © 1996 Wiley-Liss, Inc.

KEY WORDS: congenital lymphedema, atrial septal defect, hydrocele, speech delay

INTRODUCTION

Lymphedema may be congenital, acquired, isolated, or syndromal. We describe three siblings with congenital lymphedema and atrial septal defect (ASD). The parents were unaffected and clinical variability was observed within this family. To our knowledge, the association of congenital lymphedema and ASD has not been previously described.

CLINICAL REPORTS

Patient 1

P.M. was first evaluated at age 28 months. He was the 3.35 kg product of an uncomplicated term pregnancy to a 25-year-old mother. He was delivered by cesarean section for breech presentation. At birth, he was noted to have lymphedema of the lower limbs and bilateral hydrocele. A heart murmur was noted at age 5 days, which led to the echocardiographic diagnosis of a fenestrated ASD secundum. His hydroceles resolved by age 1 year, and the lymphedema of his feet improved with time.

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At 28 months he weighed 15.4 kg (75th–90th centile), was 92.5 cm long (50th–75th centile), and had a head circumference (OFC) of 49 cm (50th centile). He had a round face with a prominent forehead, normal hair consistency, epicanthal folds, upslanting palpebral fissures, flat nasal bridge with a broad nasal tip, thin upper lip, and a horizontal cleft of the chin (Fig. 1). His neck was somewhat short, but not webbed, and his internipple distance was normal. His hands were normal in appearance. At 28 months, lymphedema of the dorsum of the left foot remained, which prevented him from wearing athletic shoes with shoelaces. He also had short, deep-set toe nails (Fig. 2). His genitalia and neurological status were normal. His development has been normal except for speech delay. He has not had any brain imaging studies performed. His vision has been normal. He has not had an eye examination, nor has he had a karyotype performed. Spontaneous clo-

Fig. 1. Photograph demonstrating face of P.M.; note absence of downslanting palpebral fissures and webbed neck.

Fig. 2. Pedal edema in P.M.; the left foot is worse than right. Note transverse depressions from velcro on shoes.

sure of his ASD was documented by physical examination and echocardiogram by 3 years of age.

Patient 2

At the time of her second pregnancy the mother was 26 years old. She became pregnant while nursing P.M. The pregnancy was unremarkable until 27 weeks of gestation, when an ultrasound study demonstrated an omphalocele, severe hydrops fetalis, and oligohydramnios. The amniocentesis karyotype was normal (46,XX). On percutaneous umbilical blood sampling (PUBS), the fetal hematocrit was 29, white blood cell count was 3.02×10^{12}/liter, and platelet count was 43,000. Fetal arterial blood gas values were pO_2 of 22, pCO_2 of 43, HCO_3 of 23, and a pH of 7.33. Results of fetal liver function tests were: total bilrubin 0.6, alanine transaminase (ALT) 3, aspartate transaminase (AST) 42, and lactate dehydrogenase (LDH) 448. Cultures for parvovirus were negative. The fetus received 40 cc packed red blood cells. An intrauterine echocardiogram demonstrated massive bilateral pleural effusions and normal intracardiac anatomy, size, and function.

At 33 weeks of gestation delivery was performed by cesarean section for maternal preeclampsia. Apgar scores were 1^1 and 1^5. No resuscitation was performed (Fig. 3). Autopsy findings included a 4×4×2 cm omphalocele containing bowel; pulmonary hypoplasia (combined lung weight = 5.5 g, normal mean for gestational age = 31.8 g ± 13.5 g), an ASD, two accessory spleens, and significant extramedullary hematopoiesis in the kidney, liver, spleen, adrenal glands, and bladder. There was widespread villous edema of placenta with focally increased syncytial knots, calcification of trophoblastic basement membranes, and increased numbers of immature red blood cells. There was no villitis, viral organisms, or inclusion bodies seen in the placenta.

Patient 3

W.M. was first evaluated at 13 weeks postnatal age. He was the 4.0 kg product of an uncomplicated third pregnancy to a then 27-year-old mother. Prenatal sonographic findings were normal. Karyotype was not performed. Lymphedema of feet was noted at birth, and

Fig. 3. Autopsy photograph of case 2 demonstrating severe hydrops fetalis and omphalocele.

hydroceles and a heart murmur were noted on day 6 of life. Cardiology evaluation confirmed an ASD, secundum type.

At 13 weeks, his weight was 6.2 kg (50th–75th centile), his length was 61 cm (50th centile), and his OFC was 40 cm (50th centile). He also had a round face with prominent forehead, epicanthal folds, a wide nasal bridge, and a horizontal cleft of the chin (Fig. 4). His neck was slightly short, but not webbed. Lymphedema was noted of the dorsum of both feet (Fig. 5), and he had a bilateral hydrocele. His neurologic status is normal, and development has been normal, aside from speech delay with a pattern similar to that of his older brother. He has not had an eye examination nor brain imaging studies due to the lack of symptoms. Cardiac examination at 1 year of age revealed closure of the ASD but the additional presence of a patent ductus arteriosus. This required non-operative closure using a coil technique during cardiac catheterization.

FAMILY HISTORY

The family history was unremarkable. There was no prior history of lymphedema, birth defects, mental retardation, or fetal or neonatal deaths. Echocardiograms of both parents were within normal limits, and they had no history of heart murmur or lymphedema during childhood. The father had no history of hydrocele. The father had normal toenails. The mother had short toes and deep-set nails but no history of pedal edema in the newborn period.

DISCUSSION

Lymphedema is common at birth. It is believed to be due to temporal variation in the regression of lymphedema normally present in every fetus [Opitz, 1986]. The most common genetic form of lymphedema that

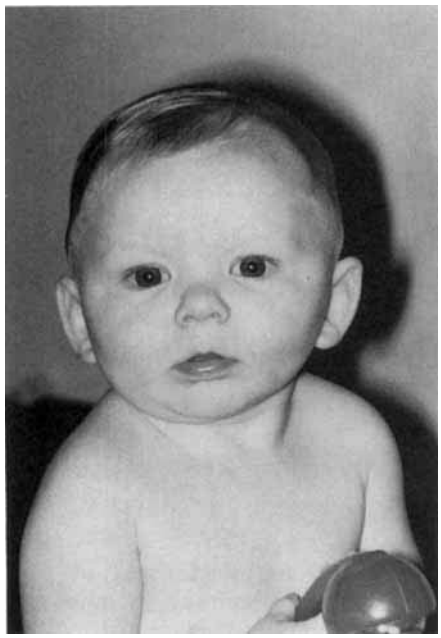

Fig. 4. Photograph demonstrating face of W.M.

presents neonatally, inherited as an autosomal dominant condition, is known as the Nonne-Milroy syndrome [Milroy, 1928; Garg, 1974]. While the lymphedema observed in our patients clinically resembles that seen in Nonne-Milroy syndrome, the presence of ASDs in all of the children and the unremarkable family history makes this an unlikely diagnosis.

Many other recognizable syndromes present with congenital lymphedema in association with other physical findings. The best known are Ullrich and Turner syndromes [Turner, 1938] and Noonan syndrome [Noonan, 1963], which usually present with swelling of the dorsum of the limbs. While ASDs have been described in Noonan syndrome [Bernier-Buzzanga and Su, 1990], the patients described here have other physical findings that set them apart. Their facial characteristics are atypical for Noonan syndrome, and they do not have short stature, webbing of the neck, or an increased internipple distance. In addition, neither parent has any physical findings that are suggestive of Noonan syndrome, which is inherited as an autosomal dominant disorder. The Hennekam syndrome, an autosomal recessive syndrome, includes lymphedema, intestinal lymphangiectasia, characteristic facial anomalies, and mental retardation [Hennekam et al., 1989; Gabrielli et al., 1991]. These traits were not observed in our patients.

Fig. 5. Photograph demonstrating severe bilateral pedal edema in W.M.

Other conditions with congenital lymphedema are distichiasis and lymphedema [Robinow et al., 1970], microcephaly and lymphedema [Leung, 1985; Crowe and Dickerman, 1986], cerebellar hypoplasia and lymphedema [Hourihane et al., 1993], lymphangiosarcoma and congenital lymphedema of an extremity [Dubin et al., 1974], and lymphedema of the legs with congenital conjunctival lymphedema [Tabbara and Baghdassarian, 1972]. Atrial septal defects have not been reported in any of these previously described conditions.

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